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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/734,786	12/11/2000	Norimitsu Saito	312762002400	4706

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MORRISON & FOERSTER LLP
3811 VALLEY CENTRE DRIVE
SUITE 500
SAN DIEGO, CA 92130-2332

EXAMINER
SULLIVAN, DANIEL M

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 10/03/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/734,786	SAITO ET AL.	
	Examiner	Art Unit	
	Daniel Sullivan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-21 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-21 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 5 .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: .

DETAILED ACTION

This is a First Office Action on the Merits of the application filed December 11, 2002, which claims priority to U.S. Provisional application 60/170,166, filed December 10, 1999.

Claims 1-21, as filed, are pending in the application.

Drawings

INFORMATION ON HOW TO EFFECT DRAWING CHANGES

1. Correction of Informalities -- 37 CFR 1.85

New corrected drawings must be filed with the changes incorporated therein. Identifying indicia, if provided, should include the title of the invention, inventor's name, and application number, or docket number (if any) if an application number has not been assigned to the application. If this information is provided, it must be placed on the front of each sheet and centered within the top margin. If corrected drawings are required in a Notice of Allowability (PTOL-37), the new drawings **MUST** be filed within the **THREE MONTH** shortened statutory period set for reply in the "Notice of Allowability." Extensions of time may NOT be obtained under the provisions of 37 CFR 1.136 for filing the corrected drawings after the mailing of a Notice of Allowability. The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.

2. Corrections other than Informalities Noted by Draftsperson on form PTO-948.

All changes to the drawings, other than informalities noted by the Draftsperson, **MUST** be made in the same manner as above except that, normally, a highlighted (preferably red ink) sketch of the changes to be incorporated into the new drawings **MUST** be approved by the examiner before the application will be allowed. No changes will be permitted to be made, other than correction of informalities, unless the examiner has approved the proposed changes.

Timing of Corrections

Applicant is required to submit acceptable corrected drawings within the time period set in the Office action. See 37 CFR 1.185(a). Failure to take corrective action within the set (or extended) period will result in **ABANDONMENT** of the application.

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Timing of Corrections

Applicant is required to submit acceptable corrected drawings within the time period set in the Office action. See 37 CFR 1.185(a). Failure to take corrective action within the set (or extended) period will result in **ABANDONMENT** of the application.

The drawings are objected to for the reasons provided on the attached PTO 948. A proposed drawing correction or corrected drawings are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance.

Specification

The disclosure is objected to because of the following informalities: the specification contains sequence that is not identified by SEQ ID No.

> "Where the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing" in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO:" in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application" 37 C.F.R. 1.821.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 9 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

The claim is drawn to a method to introduce a nucleic acid into a mammalian subject wherein said nucleic acid encodes a product that affects hair growth or quality. Given its broadest reasonable interpretation, the claim encompasses a genus of nucleic acids encoding any and all agents that affect hair growth or quality. The Revised Interim Guidelines state "when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus", "In an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus" (Column 2, page 71436). The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species, by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics (see MPEP 2163 (ii)). The specification provides only a single example of a nucleic acid encoding a protein that could affect hair color (i.e. tyrosinase). The specification fails to teach the chemical or physical structures of other nucleic acids encoding agents that affect hair growth or quality, or the common attribution of the genus of any and all nucleic acids that encode agents that affect hair growth and quality.

An adequate written description of a DNA requires more than a mere statement that it is part of the invention; what is required is a description of the DNA itself. It is not sufficient to define DNA solely by its principal biological property, i.e. it encodes a product that affects hair growth or quality, because disclosure of no more than that, as in the instant case, is simply a wish to know the identity of any DNA with that biological property. Also, naming a type of material generically known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. Thus, claiming all DNA's that achieve a result without defining

what means will do is not in compliance with the description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)). With respect to the method claims, adequate description of the methods first requires an adequate description of the materials, i.e. specific DNA sequences, which provide the means for practicing the invention.

In view of these considerations, a skilled artisan would not have viewed the teachings of the specification as sufficient to show that the applicant was in possession of the claimed invention commensurate to its scope because it does not provide adequate written description for the broad class of *any* and *all* nucleic acids encoding a product that affects hair growth and quality. Therefore, only the described nucleic acid encoding a tyrosinase meets the written description provision of 35 U.S.C. §112, first paragraph.

Claims 1-21 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the nature of the invention; (b) the breadth of the claims; (c) the state of the prior art; (d) the amount of direction provided by the inventor; (e) the existence of working examples;

(f) the relative skill of those in the art; (g) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue"; and (h) the level of predictability in the art (MPEP 2164.01 (a)).

Nature of the Invention:

Claims 1-21 are directed to compositions and methods of making and using said compositions for treating the mammalian body by means of gene therapy comprising *ex vivo* genetic modification of a histocultured organ or tissue and transplantation of the genetically modified organ or tissue into a recipient animal. Therefore the invention is directed to *ex vivo* gene therapy.

Breadth of the Claims:

The claims encompass a composition and method for delivery of an exogenous nucleic acid in the cell of a mammal *ex vivo*, through genetic modification of a histocultured organ or tissue, and thereby cover all mammals including human beings. Given that the claims are specifically drawn to a composition and methods for therapeutic or vaccination purposes and the composition and methods have no utility other than delivery of exogenous nucleic acids, the intended use for said composition is clearly gene therapy.

State of the art:

At the time of filing, gene therapy utilizing the direct administration of recombinant nucleic acids, whether in the form of retroviruses, adenoviruses, or plasmid DNA/liposome complexes, was considered to be highly unpredictable. Verma et al. states that, "[t]he Achilles heel of gene therapy is gene delivery..", and that, "most of the approaches suffer from poor efficiency of delivery and transient expression of the gene" (Verma et al. (1997) Science, Vol.

389, page 239, column 3, paragraph 2). Marshall concurs, stating that, " difficulties in getting genes transferred efficiently to target cells- and getting them expressed- remain a nagging problem for the entire field", and that, "many problems must be solved before gene therapy will be useful for more than the rare application" (Marshall (1995) Science, Vol. 269, page 1054, column 3, paragraph 2, and page 1055, column 1).

Orkin et al. further states in a report to the NIH that, " ...none of the available vector systems is entirely satisfactory, and many of the perceived advantages of vector systems have not been experimentally validated", and that," [w]hile the expectations and the promise of gene therapy are great, clinical efficacy has not been definitively demonstrated at this time in any gene therapy protocol" (Orkin et al. (1995) "Report and recommendations of the panel to assess the NIH investment in research on gene therapy", page 1, paragraph 3, and page 8, paragraph 2).

Most of the claims of the instant application are directed to compositions and methods for skin based gene therapy. To support the utility of skin based gene therapy, Applicant cites several examples of studies wherein heterologous proteins were expressed in the skin of experimental animals. Applicant cites Choate *et al.* (1996; IDS #10) wherein the genetic defect in keratinocytes from lamellar ichthyosis patients was corrected and the corrected keratinocytes produced normal epidermis when transplanted on to nude mice. Applicant also sites Deng *et al.* (1997; IDS #11) as an example of transgene expression via *ex vivo* manipulation of skin cells (i.e. keratinocytes). However, Deng *et al.* (1997; IDS#11) also teach that the difficulties encountered in other gene therapy approaches have hindered progress in developing therapies involving gene expression in skin as well, "[w]hile other tissues, such as muscle and liver, may permit longer-term gene expression by introduced retroviral vectors, epithelial tissues have

proven much less tractable in this regard" (page 1389, first paragraph of column 2) and "[w]e have regenerated corrected skin tissue *in vivo* from patients with lamellar ichthyosis and X-linked ichthyosis; however, application of such advances to the treatment of humans was blocked by an inability to sustain transgene expression *in vivo*" (page 1390, first paragraph). These teachings point out both the difficulty in obtaining sustained effective transgene expression in skin, and the unpredictability of extending success in model systems to the clinical setting.

Applicant also cites several examples gene transfer into skin with the goal of vaccinating the host against the transgene. Although the studies cited demonstrate production of antibodies resulting from gene transfer, none provide an example of the immunization sufficient to protect a mammal from a pathogen. One of the studies cited (Yu *et al.* (1999) IDS # 21) concludes with the sentence, "Further studies are required to determine the preclinical utility of this model system" (page 374, final sentence of column 2).

Among the many factors that the art teaches affect efficient gene delivery and sustained gene expression are: immune responses and the identity of the promoter used to drive gene expression. Verma *et al.* teaches that weak promoters produce only low levels of protein, and that only by using appropriate enhancer-promoter combinations can sustained levels of therapeutically effective protein expression be achieved (Verma et al., *supra*, page 240, column 2). Verma *et al.* further warns that, " ... the search for such combinations is a case of trial and error for a given type of cell" (Verma et al., *supra*, page 240, bridging sentence of columns 2-3). The state of the art is such that no correlation exists between successful expression of a gene and a therapeutic result (Ross et al Human gene Therapy, vol. 7, pages 1781-1790, September 1996, see page 1789, column 1, first paragraph). Thus, the art at the time of filing clearly establishes

that expectation for achieving a desired therapeutic effect *in vivo* by expressing a therapeutic gene using any of the expression constructs known in the art at the time of filing was extremely low.

Amount of Direction provided and existence of working examples:

As described above, the prior art teaches a method of transfecting cells and expressing exogenous nucleic acids in mammals through *ex vivo* modification of cells and tissues. However, the prior art does not teach expression of exogenous nucleic acids for the purpose of gene therapy to such levels that a therapeutic effect is obtained. In cases where prior art does not teach how to use the composition, all the guidance for using the invention must come from the specification. The specification provides guidance for adenovirus-mediated gene transfer of a reporter gene into hair follicles of histocultured mouse skin (see especially Example 1, beginning on page 11), transfer of the modified histocultured skin to a recipient mouse (see especially Example 2, beginning on page 14) and retrovirus mediated gene transfer of a potentially therapeutic gene into histocultured mouse skin. The teachings of the specification do not, however, address the art recognized barriers to achieving successful gene therapy. Transgene expression of the reporter gene *in vivo* was followed for only 10 days (page 15, line 5) and there is no teaching of a therapeutic effect associated with expression of the tyrosinase gene, even in the *in vitro* system. The specification, therefore, provides no guidance with regard to how the teachings can be used in a successful therapy.

Predictability of the Art, Amount of Experimentation and Skill level of the artisan:

While it is relatively routine in the gene transfer art to achieve expression at non therapeutic levels, i.e., expression at low levels or at levels providing no patentably useful

phenotypic effect, it is unpredictable without specific guidance and direction whether one will definitively achieve expression of a particular molecule at levels sufficient for a therapeutic effect. Thus, when there is deficiency in the art in terms of predictability of obtaining therapeutic levels of expression, the Applicant must provide sufficient guidance and direction which demonstrates or reasonably correlates to therapeutic levels of expression of a DNA product in an art recognized animal model or patient as claimed.

Even though the skill of an artisan in this subject area is considered to be very high, it would require undue experimentation on the part of an artisan to make and use the invention the invention according to its intended purpose. The specification and the examples do not provide sufficient guidance to use the claimed invention. Therefore, in the absence of specific guidance and working examples, the use of the claimed composition is unpredictable. In such a situation, one skilled in the art would not know how to use the invention as claimed, without undue experimentation. In view of the limited guidance in the specification, and limited working examples, and the unpredictability of the art, one skilled in the art would be required to engage in undue experimentation, in order to use the invention.

Thus, due to the art recognized unpredictability of achieving therapeutic levels of gene expression following direct or indirect administration of nucleic acids, the lack of guidance provided by the specification for the parameters affecting delivery and expression of therapeutic amounts of DNA into the cells using *ex vivo* gene transfer into histocultured organs or tissues, it would require undue experimentation to practice the instant invention and the skilled artisan would not have predicted success in using the claimed methods for the purpose disclosed in the

specification. Thus the specification does not enable one skilled in the art to use the claimed invention.

Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 10, 15, 17, 20 and 21 are rejected under 35 U.S.C. 102(b) as being anticipated by Li *et al.* (1997) U.S. Patent No. 5,641,508.

Claim 10 is drawn to a histocultured hair follicle, in anagen phase, modified to contain a heterologous nucleic acid molecule; claim 15 is drawn to a method of delivering a nucleic acid to a hair follicle comprising maintaining said hair follicle in histoculture and treating said histoculture with a nucleic acid; claim 17 is drawn to a method of delivering a nucleic acid to an intact tissue comprising treating a histoculture of the tissue with a said nucleic acid; claim 20 is drawn to a histoculture modified to contain a heterologous nucleic acid; and claim 21 limits the histoculture of claim 20 to an intact fragment of skin or lymph node.

Li *et al.* teaches a method of delivering a nucleic acid to a hair follicle wherein the hair follicle is comprised within a fragment of skin maintained in histoculture that is treated with said nucleic acid (see especially column 5, paragraphs l-3 for a description of the histocultured skin, and Example 3, beginning in column 26, for a description of gene transfer into the histocultured skin). Li *et al.* also teaches a histoculture modified to contain a heterologous nucleic acid wherein the histoculture is an intact fragment of skin and contains a modified hair follicle (see especially Example 3 c. "Delivery and Expression of Beta-Galactosidase Gene in Hair Follicles of Histocultured Skin" beginning in column 29, and Figure 5). Finally, in the first paragraph of

column 5, Li *et al.* teach that the histocultured skin allows the growth of hair shafts in the follicle cells, indicating that the hair follicle is in anagen phase. The modified histoculture containing a heterologous nucleic acid and method of delivering a nucleic acid to an intact histoculture taught by Li *et al.* are the same as those taught in the instant application, therefore the limitations of the claims are met by Li *et al.*

Claims 11, 13, 17 and 20 are rejected under 35 U.S.C. 102(b) as being anticipated by either one of Poston *et al.* (1998) *J Thoracic Cardiovasc. Surg.* 116:386-396 or Chapelier *et al.* (1996) *Hum. Gene Ther.* 7:1837-1845.

The limitations of claims 17 and 20 are recited above. Claim 11 is drawn to a method to introduce a nucleic acid molecule into a mammalian subject comprising transplanting into the corresponding tissue of said mammal a histocultured intact tissue that has been modified to contain said nucleic acid molecule, and claim 13 is directed to the method of claim 11 wherein the modifying step comprises treating the tissue with a liposome composition or a viral vector.

Chapelier *et al.* teaches a method of delivering a nucleic acid to intact lung tissue comprising treating a histoculture (i.e. the graft stored in a basin of physiologic saline solution) with a nucleic acid comprised within an adenovirus vector (see especially the final paragraph on page 1838). Chapelier *et al.* further teaches grafting the histocultured modified lung tissue into a recipient mammal (see especially the first paragraph on page 1839). The method of introducing a nucleic acid into an intact tissue and into a mammalian subject, as well as the histoculture modified to contain a heterologous nucleic acid, taught by Chapelier *et al.* are the same as those claimed in the instant application.

Poston *et al.* teach a method of delivering a nucleic acid to intact heart tissue comprising treating a histoculture (i.e. explanted heart in phosphate buffered saline) with a nucleic acid (i.e. antisense oligonucleotide; see especially the first full paragraph on page 388). Poston *et al.* further teaches transplanting the modified histocultured heart tissue into a recipient animal (see especially the paragraph bridging pages 387 and 388). The method of introducing a nucleic acid into an intact tissue and into a mammalian subject, and the histoculture modified to contain a heterologous nucleic acid taught by Poston *et al.* are the same as those taught in the instant application. Therefore, the limitations of the claims are met by the prior art.

Conclusion

None of the claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 703-305-4448. The examiner can normally be reached on Monday through Friday 8-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel can be reached on 703-305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are 703-746-9105 for regular communications and 703-746-9105 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

dms
September 26, 2002

JAMES KETTER
PRIMARY EXAMINER